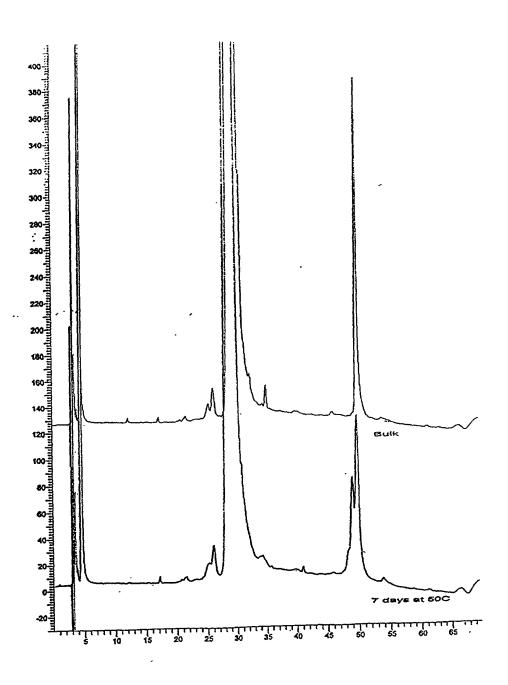
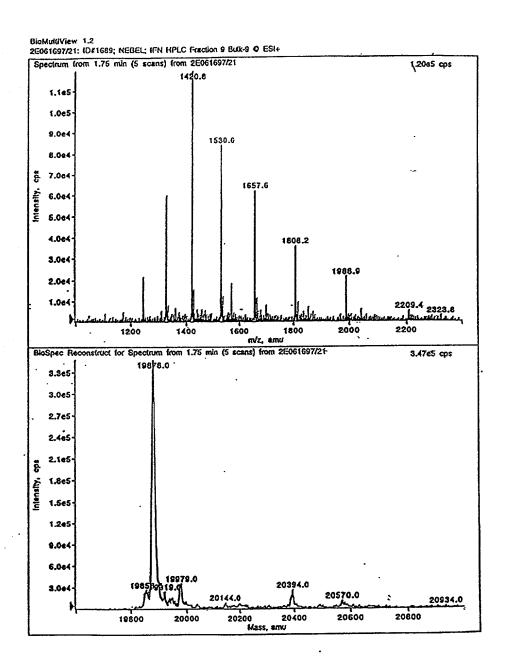
Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)



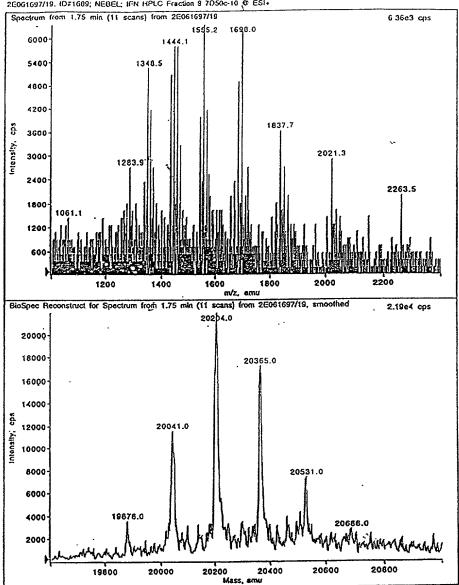
Application No: Not Assigned

Atty Dkt No: PP16166.003(35784/240745)



Inventor(s): Wolfe et al Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

BioMothView 1 2 2E0G1697/19. ID#1689; NEBEL: IFN HPLC Fraction 9 7050c-10 & ESI+



Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

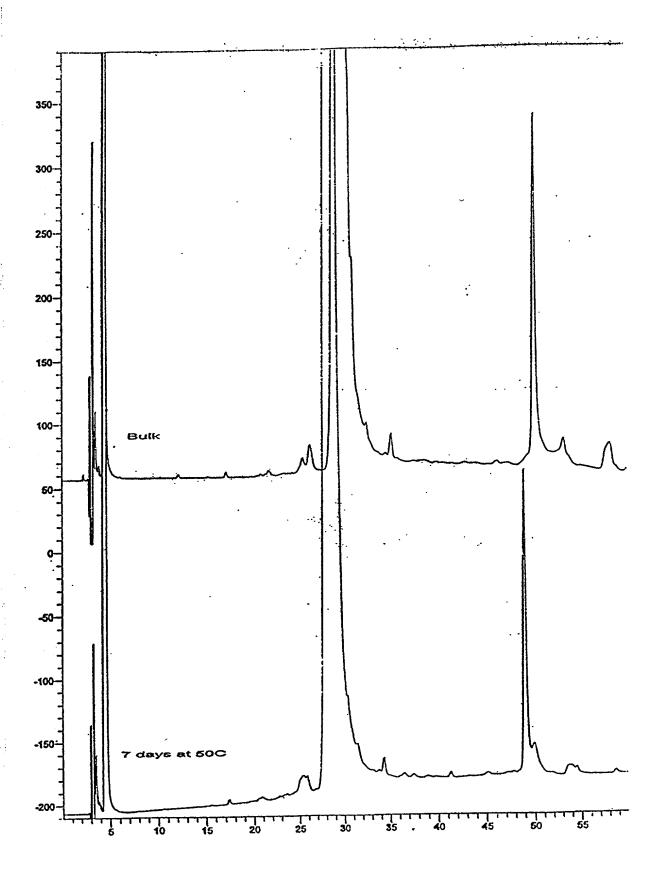
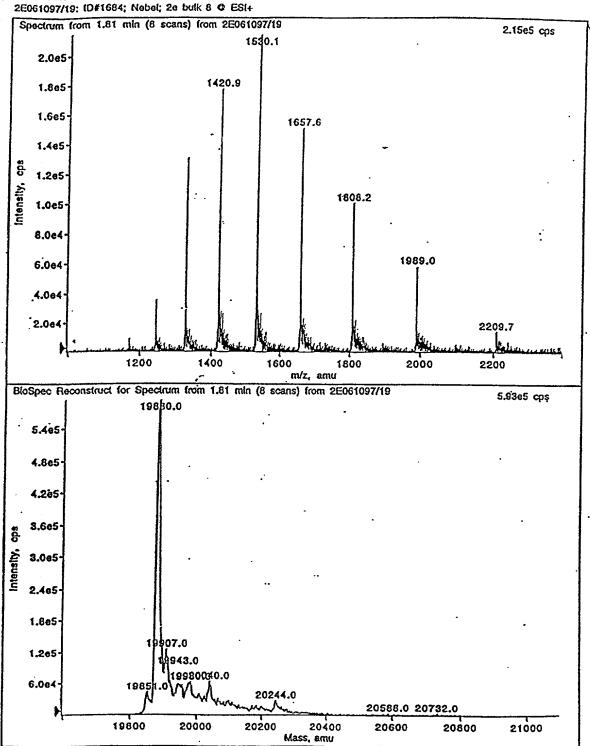


FIGURE 4

Inventor(s): Wolfe et al Application No: Not Assigned

Atty Dkt No: PP16166.003(35784/240745)

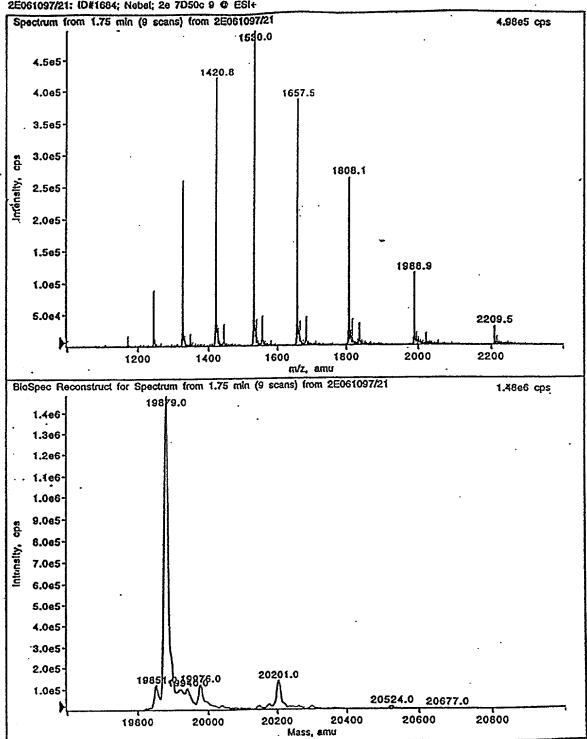
BioMultiView 1.2



Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Application No: Not Assigned

Atty Dkt No: PP16166.003(35784/240745)

- BloMuttiView 1.2 2E061097/21: ID#1684; Nebel; 2e 7D50c 9 © ESI+



Title: Stabilized Interferon Compositions
Inventor(s): Wolfe et al
Application Nor-Kasigned
Atty Dkt No: PP16166.003(35784/240745)

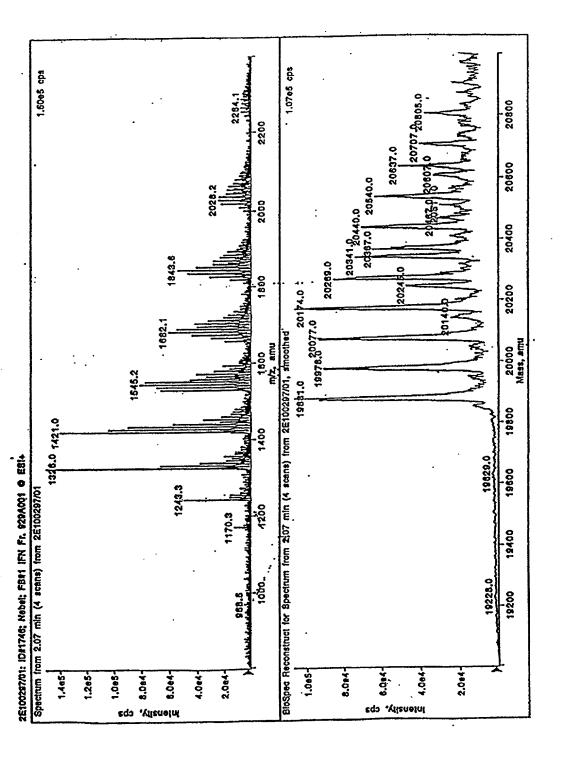
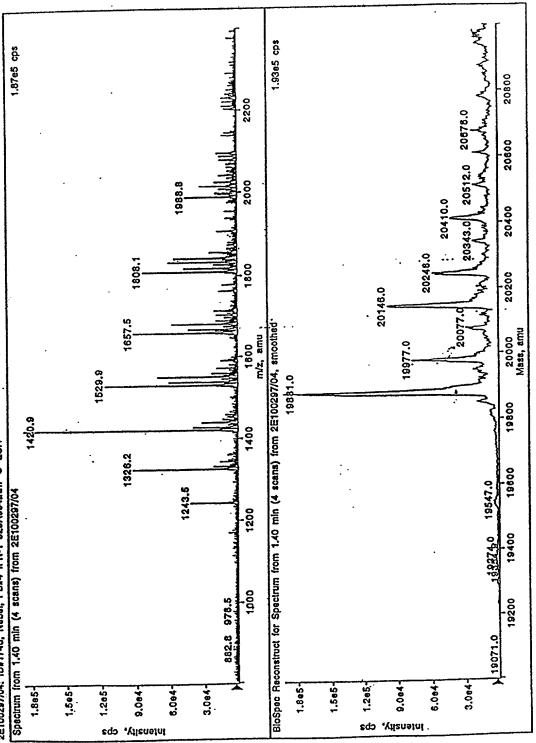


FIGURE 7

BIOMUIIVION 1.2 2E100297/04: 10#1746; Nebel; FB#4 IFN-1 929A004.28W ** © ESI+



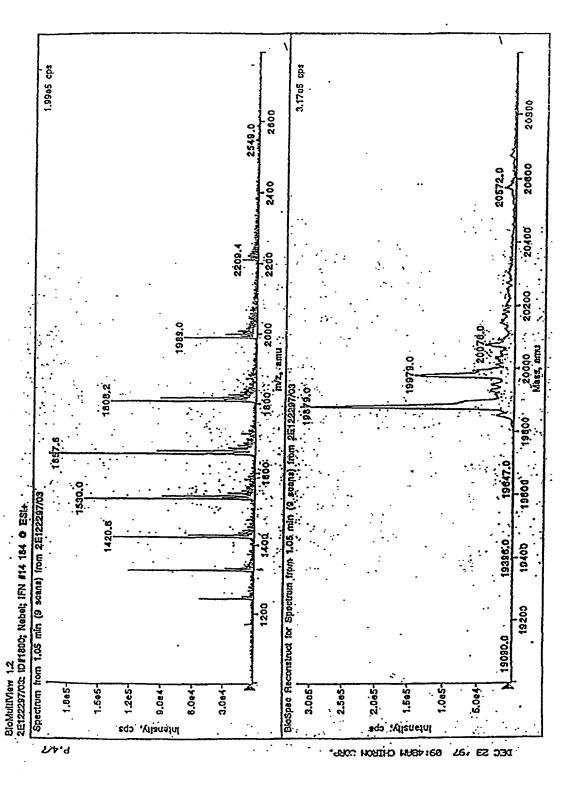


FIGURE 9

Inter. Stabilized Interferon Compositions Inventor(s): Wolfe et al Application No: Not Assigned

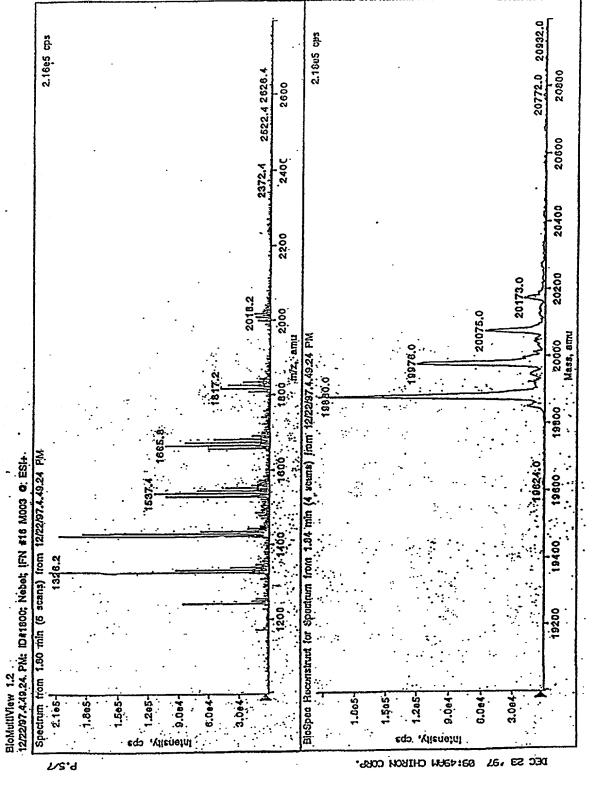


FIGURE 10

Intle: Stabilized Interferon Compositions
Inventor(s): Wolfe et al
Application No: Not Assigned

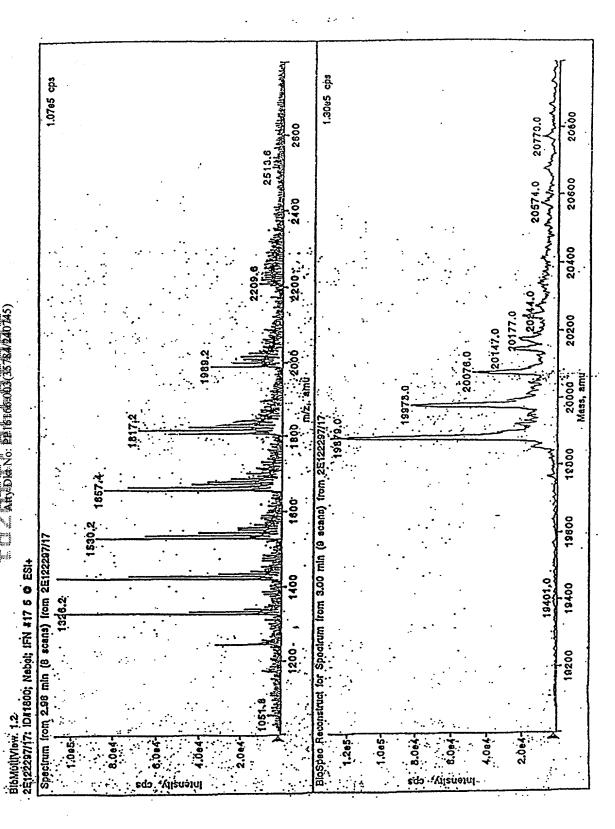


FIGURE 11

Inventor(s): Wolfe et al Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

STABILITY EVALUATION DATA

Interferon- β -1b: Dextrose Formulation

Product	Storage	Months	Potency	Glucosylated	T-4.1 ITN 10.41
Troduct	Temperature	Ivioliuis	(Specific	IFN-β-1b	Total IFNβ-1b
	(upright,		activity,	concentration	concentration
	protected from	l	IU/mg)	(mg/ml)	(mg/ml)
	light)	ļ	Tomigy	(mg/mi)	
IFN-β 1b	+ 8°C	0	2.13×10^{7}	<0.02	0.22
0.25 mg/mi	+ 8°C	1	2.50×10^{7}	<0.02	0.23
1.25 % dextrose	+ 8°C	2	2.71×10^{7}	<0.02	0.23
1.25 % HSA	+ 50°C	2.2	3.52×10^{7}	<0.02	0.23
Lot:	+ 50°C	2.5	4.68×10^{7}	Too degraded	Too degraded
MBAPM023	+ 50°C	2.7	4.60×10^{7}	Too degraded	Too degraded
7200-607	+50°C	3	5.61×10^{7}	Too degraded	Too degraded
	+8°C	3	2.41×10^{7}	<0.02	0.23
IFN-β 1b	+25°C	0	2.12×10^{7}	<0.02	0.22
0.25 mg/ml	+ 25°C	1	2.05×10^{7}	<0.02	0.21
1.25 % dextrose	+25°C	2	3.24×10^{7}	<0.02	0.22
1.25 % HSA	+ 50°C	2.2	3.88×10^{7}	<0.02	0.21
Lot:	+ 50°C	2.5	4.64×10^{7}	Too degraded	Too degraded
MBAPM027	+ 50°C	2.7	5.08×10^{7}	Too degraded	Too degraded
7200-600	+ 50°C	3	5.91×10^7	Too degraded	Too degraded
	+25°C	3	2.51×10^{7}	<0.02	0.23
IFN-β 1b	+37°C	0	2.12×10^{7}	<0.02	0.22
0.25 mg/ml	+37°C	1	2.85×10^{7}	<0.02	0.18
1.25 % dextrose	+37°C	2	3.88×10^{7}	<0.02	0.23
1.25 % HSA	+ 50°C	2.2	4.28×10^{7}	Too degraded	Too degraded
Lot:	+ 50°C	2.5	4.88×10^{7}	Too degraded	Too degraded
MBAPM027	+ 50°C	2.7	4.72×10^7	Too degraded	Too degraded
7200-600	+ 50°C	3	5.44×10^7	Too degraded	Too degraded
	+37°C	3	4.08×10^{7}	Too degraded	Too degraded

Inventor(s): Wolfe et al

Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

STABILITY EVALUATION DATA

Interferon-β-1b: Highly Purified Mannitol Formulation

Product	Storage	Months	Potency	Glucosylated	Total IFNβ-1b
Troduct	Temperature	Ivionalo	(Specific	IFN-β-1b	concentration
	(upright,		activity,	concentration	(mg/ml)
	protected from	•	IU/mg)	(mg/ml)	(5)
	light)		<u> </u>		
IFN-β 1b	+ 8°C	0	1.40×10^{7}	<0.02	0.22
0.25 mg/ml	+ 8°C	1	1.52×10^7	<0.02	0.21
1.25 % highly	+8°C	2	1.69×10^{7}	<0.02	0.22
purified	+50°C	2.2	1.68×10^{7}	<0.02	0.22
mannitol	+ 50°C	2.5	1.68×10^{7}	<0.02	0.21
1.25 % HSA	+ 50°C	2.7	1.54×10^{7}	· <0.02	0.21
	+50°C	3	1.53×10^{7}	<0.02	0.22
	+8°C	3	1.62×10^{7}	<0.02	0.23
IFN-β 1b	+25°C	0	1.40×10^{7}	<0.02	0.22
0.25 mg/ml	+25°C	1	1.58×10^{7}	<0.02	0.21
1.25 % highly	+ 25°C	2	1.88×10^{7}	<0.02	0.22
purified	+ 50°C	2.2	1.84×10^{7}	<0.02	0.22
mannitol	+ 50°C	2.5	1.67×10^{7}	<0.02	0.20
1.25 % HSA	+ 50°C	2.7	1.61×10^{7}	<0.02	0.21
	+ 50°C	3	1.53×10^{7}	<0.02	0.22
	+ 25°C	3	1.59×10^{7}	<0.02	0.23
IFN-β 1b	+37°C	0	1.40×10^{7}	<0.02	0.22
0.25 mg/ml	+37°C	1	1.50×10^{7}	<0.02	0.21
1.25 % highly	+37°C	2	1.80×10^7	<0.02	0.21
purified	+ 50°C	2.2	1.86×10^{7}	<0.02	0.21
mannitol	+ 50°C	2.5	1.84×10^{7}	<0.02	. 0.20
1.25 % HSA	+50°C	2.7	1.73×10^{7}	<0.02	0.20
	+ 50°C	3	1.41×10^{7}	<0.02	0.20
	+37°C	3	1.53×10^{7}	<0.02	0.22

Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al

Application No: Not-Assigned Transfer of the State of

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MEDPHING (MANNITOL FORMULATION)

		i																								
	Sterllity		Pass		:	ł	1	:	ı	ı	1	ı	Pass		í	1	1	J	ı	1	1	·	i	Pass	Ž	Ì
	Folency Confutner Closure Integrity	DJEJKAR KEST	1	;	: 1	;	ŧ	•	i	2	1	ł	Pass		ŧ	1	• •	:	1	;		ı	•	Pass	Pass	
	Potency	(IUling x 10 ⁷)	23		2.8	:	i 1	1 7	ţ :	7 .	7:	ว :	ដ		1 ;	Ť	:	:	3.1	. 15		:	3	E	22 to 45 x 107	
	pH Upon Reconstitution		7.4	;	7.3		. 1	7	, t		, ,	t (7.5	1	; ;	3	ŧ	;	7.4	7.5	7.	7.	ξ ;	7.4	7.1-7.8	
	Residual	(% by weight)	0.3	ŧ	0.5	7 0		70	9.5	Š	, Y	3 ;	970	10	, y	9 6	ę P	ı	<u>6,7</u>	0.8	80	9	1 ;	11	Nort 3%	
	Upon Recon. Color		t	ŧ	•	1	1	ŧ	;	:	coloriese	200.0	>HX)	1	ς. ΥΒΑ,	į	ı	1	HY.	&¥.	ı	colorless		58 %	Colorfest to	slightly yellow NMTBY,
redge	Upon Recon.		:	1		1	:		:	:	п	ŧ	7	ŧ	₽	1	}		₹	₹	1	₹	Ę	Į	NMTRefill	
Appearence	Upon Reconstitution		clear, slightly yellow	i	clear, colorless	:	:	clear, coloriess	clear, colorless	clear, coloriess	clear, slightly rellow	clear ellohele mellone	words suggest & comme	ı	clear, colodess		1	1	cient, alightly yellow	clear, colorless	clear, colorless	cicar, alightly yellow	Alama affaltedia analyzana	ciest, mighing yearsw	Clear,	colariess to light yellow
	Plug (cake)		white	:	white	:	;	white	Thirt	white	white	white		ŧ	while	1	1	;	Athre	white	white	white	uhika		White	
	Months in Starage		0	8	m	4	ν	ψ	0	ဌ	81	24	ì	14	m	4	· (/		۵	Φ.	ដ	₩	74	.	European Specifications:	
	Morage Temp.	Đ		*	4	*	4	4	*	4	4	4		R	គ	R	æ	: 8	2	ଛ	유	읎	22	3	Ekropean	

FIGURE 14(A)

Title: Stabilized Interferon Compositions
Inventor(s): Wolfe et al
Inventor(s): Wolfe et al
Application: Wolfe et al
Application: Wolfe et al
Application: Wolfe et al
Application: No: PP16166.003(35784/240745)

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MBDPN006 (MANNITOL FORMULATION)

ils	Peak B 1	(mg/m)	į	1	1	:	20.0	<0.02***	<0.02***	40.02	0.02	<0.02	t		•	<0.02	<0.02***	<0.02***	<0.02	<0.02	40.02
RP-HPLC-Analysis	interferon beta-1d (Peak B + Peak B1)	(lm/gm)	ŧ	1	1	ţ	0.24	0.25***	0.23***	0.23	0.25	0.25	1	ŧ	ţ	0.23	0.25***	0.23***	0.23	0.24	0.24
•	Months in Storage	4	0	7	m	4	หา	vo	6.	ជ	8 2	24	И	**	4	'	ø	Φ.	ᄗ	<u>8</u>	74
,	Storage Temp.	(0.)	^	•	4	4	ঘ	4	4	4	4	귝	33	30	20	30	8	30	8	8	e

FIGURE 14(B)

Expected Results: 0.25 ± 0.04 NMT 0.02 *** SOP QG162 (AKA Q1052) was not followed: NLT one injection per test vial (two test vials per kg) was not performed.

Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al.

Typication with Assigned Typication Atty Dkt No: PP16166.003(35784/240745)

STABILITY OF BETASERON J BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MEDPNOUS (MANNITOL FORMULATION)

	Steedlity		Pass		ŧ	:	:	ŧ	:	:	:	ı	Pass		•	;	ı		ı	ı	ı	ı	ł	Pass		P. C.
	Container Govern Integrity Doe Leak Teet		ï	;	! :	! ;	!	•	ŧ	i	1	1	Poss			1	ı	!	! :		ł	1	:	Pass		254
	Fotency CPE Bloasny	(TUME x 107)	2.9	1	. 2.7	: 4	: :	: ;	7 .	¢ (7 (7.8	33		: ;	3.0	1	2	34	3.4		4.0	2.9	32	Townson of	01 × C+ m +->
	pH Upon Reconstitution		7.3	1	7.4	:	1	¥.		2 4	9 4	ą	7.6		, ;	Ç	ı	ł	7.5	972	3.6	2 6	q	7.6	21.7*	3
	Recident . Molsture	(% by weight)	63	0.5	0.5	5:0	: \$	ķ	9 6) Y	3 5	3	970	5	5 6	3	9.0	1	0.7	9	00	3 5	3	1.1	NATTAK	
	Upon Recon. Calar		:	i			:	ı	1	ı	coloclere	***************************************	>BY,	;	: ;	:	ŧ	ī	BY	48¥	•	mimies		>BY,	Colorlese to	slightly yellow BY.
cance	Upon Recon. Clarity		1	i		1	:	:	:	ŧ	₹	, 1	₹	1	É	ş	1	:	₩	ㅁ		E	(₹	MATRETH	
Арреяся	Upon Reconstitution		ciçar, colorless	ı	clear, colothess	:	•	clear, coloriess	clear, colorless	cleur, colodess	clear, coloriess	10 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	cleat, alignity yellow	ı	clear, colorless		1	ľ	clear, slightly yellow	clear, colociess	clear,poloriess	cierrodorless		clear, sugniy yellow	Cler	coloriess to light yellow
	rage Greek		white	1	#hite	ŧ	1	white	*Eite	white	white	***	Miller	ŧ	white	:		: ;	White	apic.	white	white	A. A.	Author	White	
•	Months in Storage		0	ч	m	₹ '	₩	ø	Φ	2	3 8	7	\$	7	eri	4	. 4	٠,	·o	Φ	ជ	#	7.	\$	Emopean Specifications:	
,	Storage Temp.	ပို		4	*	.	-	~	~	*	*	¥	t	គ	R	33	5	3 8	क्ष	묶	R	R	ç	ñ	Empen S	

FIGURE 15(A)

Inventor(s): Wolfe et al

The standard of the

Title: Stabilized Interferon Compositions

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MEDPINGS (MAINITOL FORMULATION)

lysis.	Peak B1 februsylated)	(ms/m)	1	i	.1	,	20.02	<0.02***	40.02	-0.05 -0.05	60.02	40.02	1	ł	1	<0.02	<0.02***	<0.02***	<0.02	<0.02	20:0>
RP-HFLC Analysis	Interferon beta-1b (Peak B+ Peak B1)	(mg/ml)	ı	ŧ	•	;	0.23	0.24***	0.23***	0.23	0.24	0.25	1	1	:	0.23	0.24***	0,22***	0.22	0.23	0.23
	Months in Storage		٥	ч	m	4	*1	9	ø	건	<u>≈</u>	*	8	m	₹.	٧٦	9	σ,	검	62	*
	Storage Temp.	(p _e)	~	4	マ	4	4	4	4	4	ਚ ੰ	4	200	30	30	30	30	30	30	30	ଜ

Expected Results:

**** SOP QG162 (AKA Q1052) was not followed: NLT one injection per test vial (two test vials per lot) was not performe
Note: A correction was made to the 18 month data point for RP-HPLC.

FIGURE 15(B)

Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al.

The line of the stable of the s

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MEDPINGG (MANNIFOL FORMULATION)

	Container Closure Integrity	A) Checks And		l	i	I	1		1	į	ı	1	f	1	Pace			:	ſ		l	1	ı		ľ	1	1	Pass		Pice	}
	Potency CPE Binguay	(IU/mg x 107)	0.6	!	:	2.9	ì	}	1	23	2	ì	3.5	52	3.2		i	ŧ	32	:		;	2.4	3.2	ļ .	7.5	3.1	333		2.2 to 4.5 x 107	
	pH Upon Reconstitution		13		1	7.3	;		:	L T	7.4	2.6	5	7.5	7.2		ı	: ;	7.3	ŧ	;	١,	7.4	7.5	7.4	ţ ;	\$	7.4		7.1.7.8	
	Residual Molsture	(% by weight)	\$,	0.5	0.5	0.5	1	1	ž	9.0	0.5	! ;	8	979		90	2	2	0.5	1		Ç	å7.	S	: :	3.	3		NMT3%	
	Upon Recon. Color		1		1		:	•		1	:	ŧ	colostes	* COLOROS	>BY,		i	1		1	:	1	ì	•	1	emineless	28V.	427		Coloness to	All Entry yellow
Appearance	Upon Recon. Charity	•	:	;	ì	ı	i	1	1	1	1	ı	₹	! {	₹		1	;	;	ı	:	ŧ	1	1	ŧ	Ħ	ij	1	MACTORACOTTO	THAT YES IT	
	Upon Reconstitution		clear, colorless	N/A	clear Animalese	A764		NA.	clear, slightly vellow	Clear mindees		מכינה" במוסגונים	clear, colociess	cless wijohilw wellow	אייייי בייליוויל לייייי	. ***	WAY	clear, coloriess	NA	424		clear, alightly yellow	clerrenteres	Clear colosfore	Storming of the state of the st	Clear, colorless	clear, slightly yellow		Clear	coloriess to light wellow	
	Plug (cales)		white	NA	white	N. N.	Y.X	SAT	white	white	whire	417	ALUM.	white		NA		MILE	XX.	N/A		wille	white	white	T.	3077	White		White		
	Temp. Storage		.	4	₩.	*	*	. ,	**	4	4 12		or ·	74		30	30	n :	30	30 5	30	3	30 05	30 51					European Specification	t	

FIGURE 16(A)

Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Inventor(s): Wolfe et al Application No: Noff-Assigned Interferon Compositions Atty Dkt No: PP16166.003(35784/240745)

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT RESULTS FOR LOT MEDPHOÜ (MANNITOL FORMULATION)

alysis		(Edwards)	(1111/2011)	•		?	:	1	2000	76:00		<0.02***	40.02	40.02	<0.02		f	£	3	\$1 CV	***************************************	*****	1 8	7000	70.05	40.02
RP-HFLC Analysis	interferon beta-Ib (Reak B+TeakB1)	(me/m)	fam. A3	1		1	1	ı	0.24	0.954**	****	2	0,23	0.25	0.25	i		3	!	0.22	0.25***	0.24**	0.23	200	700	4770
•	Months in Storage			o	r	٧.	m •	4	*^	•9	. 0	>	ជ	∞	**	14	. *	n .	4	**	v	•	ជ	**	75	i
ć	Storage Temp.	(3.)	•		~	٠.	4	4	4	4	4		₹ '	4	4	30	5	3 1	R	8	R	20	유	e	S	1

Expected Results:

*** SOP QGIGZ (AKA QIGSZ) was not followed: NLT one injection per test vial (two test vink per 10f) was not performed

Note: A correction was made to the 18 month data point for RP-HPLC.

FIGURE 16(B)

Title: Stabilized Interferon Compositions Inventor(s): Wolfe et al Application No: Not Assigned Atty Dkt No: PP16166.003(35784/240745)

REDUCING ACTIVITY IN MANNITOL SAMPLES

Sample	Sample	Reducing Activity	Mean Value
No.		Content (ppm)	(ppm)
1	Sample # 1 Unpurified	53.7	
2	Sample # 2 Unpurified	44.1	44.1
3	Sample # 3 Unpurified	34.4	
4	Sample # 1 Methanol Treated	19.3	
5	Sample # 2 Methanol Treated	19,2	18.5
6	Sample # 3 Methanol Treated	17.0	
7	Highly Purified Mannitol # 1	10.5	
8	Highly Purified Mannitol # 2	11.2	10.2
9	Highly Purified Mannitol # 3	8.9	